

REMARKS

Claims 1-160 were pending. Upon entry of this amendment, claims 1, 21, and 157-161 will be pending. Accordingly, two (2) independent claims and six (6) dependent claims are pending.

This amendment cancels claims 2-20 and 22-156, replaces claims 1, 21, and 157-160 with correspondingly numbered claims, and adds new claim 161, support for which is found on page 38, lines 5-22 of the specification. No new matter has been added.

A version of the claims with markings to show where changes have been made appears in Appendix A at the end of this communication.

During a telephonic interview, the Examiner requested Applicants to re-provide pages 350-866 of the specification.

Accordingly, Applicants are pleased to provide the pages requested by the Examiner.


CONCLUSION

Allowance of claims 1, 21, and 157-161 is respectfully requested.



ABBOTT LABORATORIES
Telephone: (847) 937-3810
Facsimile: (847) 938-2623

Respectfully submitted,
Winn, et al.


B. Gregory Donner
Registration No. 34,580
Attorney for Applicants

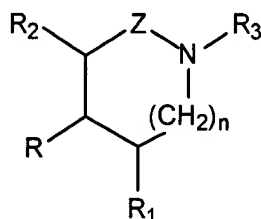


Appendix A
VERSION OF CLAIMS WITH MARKINGS TO SHOW CLANGES MADE

U.S. Application Ser. No. 09/653,563

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1 (Amended). A compound of the formula:



wherein

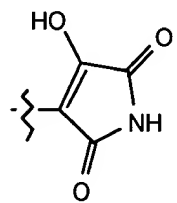
Z is -C(R₁₈)(R₁₉)- [or -C(O)-] wherein R₁₈ and R₁₉ are [independently selected from]
hydrogen [and loweralkyl];

n is 0 [or 1];

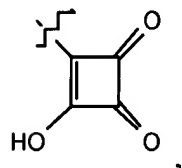
R is -(CH₂)_m-W wherein m is [an integer from] 0 [to 6] and W is

- [(a)] -C(O)₂-G wherein G is hydrogen [or a carboxy protecting group,
- (b) -PO₃H₂,
- (c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,
- (d) -CN,
- (e) -C(O)NHR₁₇ wherein R₁₇ is loweralkyl,
- (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,
- (h) tetrazolyl,
- (i) hydroxy,
- (j) alkoxy,
- (k) sulfonamido,
- (l) -C(O)NHS(O)₂R₁₆ wherein R₁₆ is loweralkyl, haloalkyl, aryl or
dialkylamino,

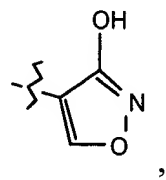
(m) $-\text{S}(\text{O})_2\text{NHC}(\text{O})\text{R}_{16}$ wherein R_{16} is defined as above,



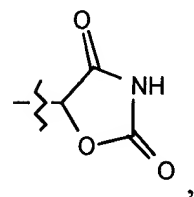
(n) ,



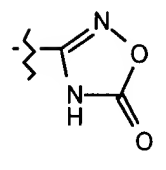
(o) ,



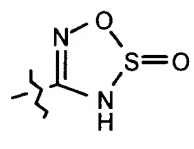
(p) ,



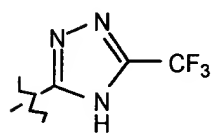
(q) ,



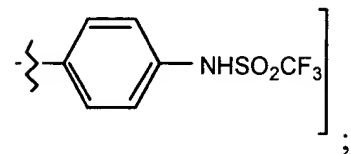
(r) ,



(s) ,



(t) , or



(u) ;

R_1 and R_2 are independently selected from the group consisting of [hydrogen,] loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl,

haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene[, with the proviso that one or both of R_1 and R_2 is other than hydrogen]; **and**

R_3 is [(a)] $R_4-C(O)-R_5-$ [, $R_4-R_{5a}-$, $R_4-C(O)-R_5-N(R_6)-$, $R_6-S(O)_2-R_7-$ or $R_{26}-S(O)-R_{27}-$]

wherein R_5 is [(i) a covalent bond, (ii)] alkylene[, (iii) alkenylene, (iv)

$-N(R_{20})-R_8-$ or $-R_{8a}-N(R_{20})-R_8-$

wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene] and [alkenylene and

R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or

(v) $-O-R_9-$ or $-R_{9a}-O-R_9-$

wherein R_9 and R_{9a} are independently selected from alkylene;

R_{5a} is (i) alkylene or (ii) alkenylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})-R_{10}-$ or $-R_{10a}-N(R_{21})-R_{10}-$

wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;]

R_4 [and R_6 are independently] **is** selected from the group consisting of

(i) $(R_{11})(R_{12})N-$ wherein R_{11} **is hydrogen** and R_{12} [are independently] **is** selected from **the group consisting of**

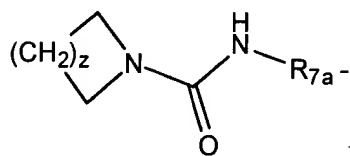
- [(1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12)] arylalkyl,
- [(13) (heterocyclic)alkyl,
- (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl,
- (17) trialkylaminoalkyl,
- (18) alkylaminoalkyl,
- (19) dialkylaminoalkyl,] and
- [(20) carboxyalkyl]

diarylalkyl

and

- (ii) [loweralkyl,
- (iii) alkenyl,
- (iv) alkynyl,
- (v) cycloalkyl,
- (vi) cycloalkylalkyl,
- (vii) aryl,
- (viii) arylalkyl,
- (ix) heterocyclic,
- (x) (heterocyclic)alkyl,

- (xi) alkoxyalkyl,
- (xii) hydroxyalkyl,
- (xiii) haloalkyl,
- (xiv) haloalkenyl,
- (xv) haloalkoxyalkyl,
- (xvi) haloalkoxy,
- (xvii) alkoxyhaloalkyl,
- (xviii) alkylaminoalkyl,
- (xix) dialkylaminoalkyl,
- (xx) alkoxy, and



(xxi) where z is 0-5 and R_{7a} is alkylene;]

$(R_{11a})(R_{12a})N-N(H)-$ wherein R_{11a} and R_{12a} are independently

selected from the group consisting of aryl and alkyl

[R_{26} is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and

R_{27} is alkylene or alkenylene;

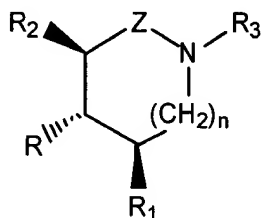
(b) $R_{22}-O-C(O)-R_{23}-$ wherein R_{22} is a carboxy protecting group or heterocyclic and R_{23} is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{24})-R_{25}-$ wherein R_{25} is alkylene and R_{24} is hydrogen or loweralkyl,

- (c) loweralkyl,
- (d) alkenyl,
- (e) alkynyl,
- (f) cycloalkyl,
- (g) cycloalkylalkyl,

- (h) aryl,
- (i) arylalkyl,
- (j) aryloxyalkyl,
- (k) heterocyclic,
- (l) (heterocyclic)alkyl,
- (m) alkoxyalkyl,
- (n) alkoxyalkoxyalkyl, or
- (o) $R_{13}-C(O)-CH(R_{14})-$ wherein R_{13} is amino, alkylamino or dialkylamino
and R_{14} is aryl or $R_{15}-C(O)-$ wherein R_{15} is amino, alkylamino or
dialkylamino];

or a pharmaceutically acceptable salt thereof.

21 (Amended). The compound according to [C]claim 1 of the formula:



[wherein

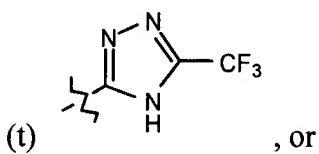
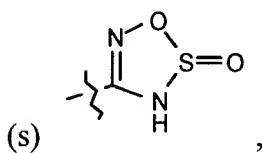
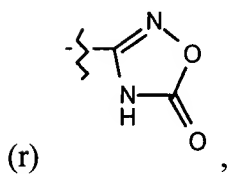
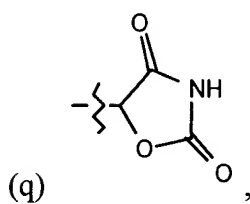
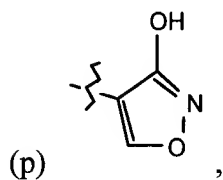
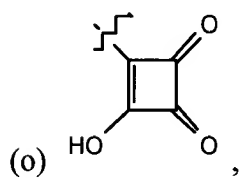
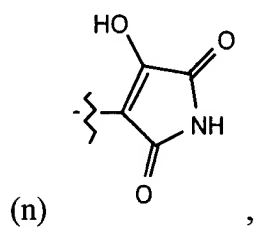
Z is $-C(R_{18})(R_{19})-$ or $-C(O)-$ wherein R_{18} and R_{19} are independently selected from hydrogen
and loweralkyl;

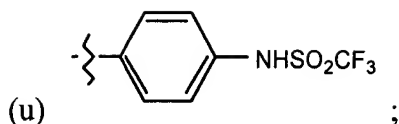
n is 0 or 1;

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

- (a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
- (b) $-PO_3H_2$,
- (c) $-P(O)(OH)E$ wherein E is hydrogen, loweralkyl or arylalkyl,
- (d) $-CN$,
- (e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,
- (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,

- (h) tetrazolyl,
- (i) hydroxy,
- (j) alkoxy,
- (k) sulfonamido,
- (l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,
- (m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,





R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyacetylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and (R_{aa})(R_{bb})N-R_{cc}- wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is (a) R₄-C(O)-R₅-, R₄-R_{5a}-, R₆-S(O)₂-R₇- or R₂₆-S(O)-R₂₇-

wherein R₅ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) -N(R₂₀)-R₈- or -R_{8a}-N(R₂₀)-R₈-

wherein R₈ and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R₂₀ is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) -O-R₉- or -R_{9a}-O-R₉-

wherein R₉ and R_{9a} are independently selected from alkylene;

R_{5a} is (i) alkylene or (ii) alkenylene;

R₇ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R₂₁)-R₁₀- or -R_{10a}-N(R₂₁)-R₁₀-

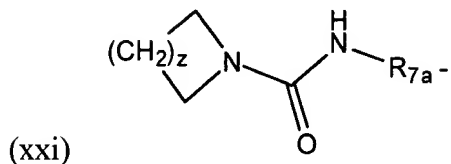
wherein R₁₀ and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R₂₁ is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₄ and R₆ are independently selected from the group consisting of

- (i) (R₁₁)(R₁₂)N- wherein R₁₁ and R₁₂ are independently selected from
 - (1) hydrogen,
 - (2) loweralkyl,

- (3) haloalkyl,
 - (4) alkoxyalkyl,
 - (5) haloalkoxyalkyl,
 - (6) alkenyl,
 - (7) alkynyl,
 - (8) cycloalkyl,
 - (9) cycloalkylalkyl,
 - (10) aryl,
 - (11) heterocyclic,
 - (12) arylalkyl,
 - (13) (heterocyclic)alkyl,
 - (14) hydroxyalkyl,
 - (15) alkoxy,
 - (16) aminoalkyl, and
 - (17) trialkylaminoalkyl,
-
- (ii) loweralkyl,
 - (iii) alkenyl,
 - (iv) alkynyl,
 - (v) cycloalkyl,
 - (vi) cycloalkylalkyl,
 - (vii) aryl,
 - (viii) arylalkyl,
 - (ix) heterocyclic,
 - (x) (heterocyclic)alkyl,
 - (xi) alkoxyalkyl,
 - (xii) hydroxyalkyl,
 - (xiii) haloalkyl,
 - (xiv) haloalkenyl,
 - (xv) haloalkoxyalkyl,
 - (xvi) haloalkoxy,
 - (xvii) alkoxyhaloalkyl,

- (xviii) alkylaminoalkyl,
- (xix) dialkylaminoalkyl,
- (xx) alkoxy, and



wherein z is 0-5 and R_{7a} is alkylene;

R₂₆ is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and

R₂₇ is alkylene or alkenylene;

- (b) R₂₂-O-C(O)-R₂₃- wherein R₂₂ is a carboxy protecting group or heterocyclic and R₂₃ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R₂₄)-R₂₅- wherein R₂₅ is alkylene and R₂₄ is hydrogen or loweralkyl,
- (c) loweralkyl,
- (d) alkenyl,
- (e) alkynyl,
- (f) cycloalkyl,
- (g) cycloalkylalkyl,
- (h) aryl,
- (i) arylalkyl,
- (j) aryloxyalkyl,
- (k) heterocyclic,
- (l) (heterocyclic)alkyl,
- (m) alkoxyalkyl,
- (n) alkoxyalkoxyalkyl, or
- (o) R₁₃-C(O)-CH(R₁₄)-

wherein R₁₃ is amino, alkylamino or dialkylamino and R₁₄ is aryl or R₁₅-C(O)-
wherein R₁₅ is amino, alkylamino or dialkylamino;
or a pharmaceutically acceptable salt thereof].

157 (Amended). [A] **The** compound according to claim 1 [of formula (I)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is aryl substituted with one substituent selected from **the group consisting of** methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from **the group consisting of** arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl].

158 (Amended). [A] **The** compound according to claim 1 [of formula (I)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is phenyl substituted with one substituent selected from **the group consisting of** methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from **the group consisting of** phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl].

159 (Amended). [A] **The** compound according to claim 21 [of formula (II)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is aryl substituted with one substituent selected from **the group consisting of** methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from **the group consisting of** arylalkyl and

diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl[; and one of R_{11a} or R_{12a} is alkyl and the other is aryl].

160 (Amended). [A] **The** compound according to claim 21 [of formula (II)] wherein [n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen;] R₁ is phenyl substituted with one substituent selected from **the group consisting of** methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; [R₃ is R₄-C(O)-R₅- wherein] R₅ is methylene; [and R₄ is selected from (R₁₁)(R₁₂)N-] and [(R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and] R₁₂ is [hydrogen and the other is] selected from **the group consisting of** phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl[; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl].